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10/534,774	12/08/2005	Sara Brett	VB60547	1360

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
12/24/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/534,774	BRETT ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-19* is/are pending in the application.

4a) Of the above claim(s) *7,8,12,13,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 9-11 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 15 September 2008. Claims 14 and 20 have been cancelled. Claims 1-13 and 15-19 are pending. Claims 7, 8, 12, 13, 18 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 1-6, 9-11 and 15-17 are currently examined.

Claim Objections

The objections to the specification and claim 9-11 are withdrawn in response to Applicant's amendment.

Double Patenting

The provisional nonstatutory double patenting rejection of claim 1 as being unpatentable over claim 10 of copending Application No. 10/535,047 is **maintained** until Applicants submit a compliant terminal disclaimer.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-6, 9-11 and 15-17 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification commensurate in scope is withdrawn in response to Applicants' amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

I. The rejection of claims 1-5, 15 and 16 under 35 U.S.C. §103(a) as being obvious over Chien *et al.* (US 6,261,764 B1, 17 July 2001, "Chien") in view of Glenn *et al.* (US 2006/0199174 A1, effectively filed on 22 August 2003) is **maintained**.

The instant claims are directed to a codon-optimized HCV polynucleotide of two expression cassettes in cis, the first expression cassette encoding the HCV core protein is downstream of the second expression cassette encoding at least one other HCV protein.

Chien discloses a DNA expression cassette encoding the HCV proteins, NS3-NS4B-NS5B-core, wherein the core protein is a truncated fragment consisting of amino acids 10-53 downstream of the nonstructural (NS) proteins and the nonstructural proteins contain multiple epitopes (column 5, line 11-53), which meets the limitation of mutated core protein wherein the mutation reduces expression of the core protein.

Chien does not disclose the core protein in a second expression cassette and is implicit on the part that the epitopes encoded by the DNA cassette are codon-optimized.

Glenn discloses that single and dual expression cassette vectors are well known in the art (page 8, paragraph [0073]). Glenn also suggests codon optimization of HCV nucleic acids or polynucleotides for expression in mammalian cells (page 8, paragraph [0072]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Chien polynucleotides so as to include a second expression cassette encoding the truncated core protein and optimize the codons of the polynucleotides for expression in cells of mammalian cells. The skilled artisan would have been motivated to do so to ensure that the core protein is expressed at the same time as the nonstructural HCV fusion proteins (NS4B-NS5B) but as a separate protein in the same cell. This way, both anti-core and anti-NS immune responses can be simultaneously elicited and/or detected. There would have been a reasonable expectation of success, given the art-recognized practice of DNA plasmids with dual expression cassettes, as taught by Glenn. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

II. The rejection of claims 1-6, 9-11 and 15-17 under 35 U.S.C. §103(a) as being obvious over Chien *et al.* (US 6,261,764 B1, 17 July 2001, "Chien") in view of Glenn *et al.* (US 2006/0199174 A1, effectively filed on 22 August 2003) and Shah et al. (US 6,727,092 B2, filed 17 July 2002, herein after "Shah") is **maintained**.

The instant claims are directed to a codon-optimized HCV plasmid of two expression cassettes *in cis*, the first expression cassette, encoding NS3 fused to a C-terminal truncated HCV core protein consisting of amino acids 1-151, is downstream of the second expression cassette encoding NS4B-NS5B fusion protein.

Chien discloses a DNA expression cassette encoding the HCV proteins, NS3-NS4B-NS5B-core, wherein the core protein is a truncated fragment consisting of amino acids 10-53 downstream of the nonstructural (NS) proteins and the nonstructural proteins contain multiple epitopes (column 5, line 11-53).

Chien does not disclose the HCV core protein in a second expression cassette, nor the fusion of HCV NS3 with a truncated core protein consisting of amino acids 1-151. Chien is implicit on the part that the epitopes encoded by the DNA cassette are codon-optimized.

Glenn discloses that single and dual expression cassette vectors are well known in the art (page 8, paragraph [0073]). Glenn also suggests codon optimization of HCV nucleic acids or polynucleotides for expression in mammalian cells (page 8, paragraph [0072]).

Glenn does not disclose the fusion of HCV NS3 with a truncated core protein consisting of amino acids 1-151.

Shah discloses a plasmid containing codon-optimized sequences of an HCV NS3 segment fused to an HCV core region of amino acids 1-150 (column 18, line 9-12). Shah further discloses that multiple epitopes have been identified within the first 115

amino acids of the native HCV core protein and suggests that recombinant antigens for the detection of anti-core immune responses need only contain this portion of the native protein (column 15, line 34-42).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Chien polynucleotides so as to include a second expression cassette encoding the truncated core protein and optimize the codons of the polynucleotides for expression in cells of mammalian cells. The skilled artisan would have been motivated to do so to ensure that the core protein is expressed at the same time as the nonstructural HCV fusion proteins (NS4B-NS5B) but as a separate protein in the same cell. This way, both anti-core and anti-NS immune responses can be simultaneously elicited and/or detected. There would have been a reasonable expectation of success, given the art-recognized practice of DNA plasmids with dual expression cassettes, as taught by Glenn.

It would have been further obvious to one of ordinary skill in the art at the time the invention was made to modify the Chien polynucleotides so as to include a second expression cassette encoding the NS3B tether to a truncated core protein of amino acids 1-150, as taught by Shah. The skilled artisan would have been motivated to do so to optimize the expression of all four antigens so as to increase the amount of immune response, especially since the NS3-core(1-150) is routinely used in multiple commercial assays for the detection of HCV, as taught by Shah.

The Shah HCV core protein fragment (amino acids 1-150) differs from the claimed HCV core fragment (amino acids 1-151) by only one amino acid residue, which renders the claimed invention obvious since the minor change in chemical configuration or design of molecule discovered or made by applicants is *de minimis*, since there is no evidence that amino acid 151 of HCV core protein is essential for immunogenic activity, and since applicants have not explained practical advantages of any differences in the structure between claimed HCV core protein fragment and the prior art. See *Ex Parte Anderson* 30 USPQ2d 1866 (Bd, Pat, App, & Int, 1993).

Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant's response has condensed the traversal of the two prior art rejections into one general discussion rather than directing arguments to each specific rejection. Therefore, Applicants' arguments have been addressed in one discussion to the extent that they read on each of the two rejections under 35 U.S.C. §103.

Applicant argues that Chien does not disclose an immunogenic composition. Examiner does not concur. Chien specifically discloses a composition comprising at least one HCV antigen (see claim 28 in column 14) to generate antibodies for detection in an assay, which meets the claim limitation of an immunogenic composition.

Applicant additionally argued that Chien does not disclose a first and a second expression cassette encoding HCV core protein downstream from other HCV proteins, which Examiner completely agrees. However, this argument mischaracterizes the rejection because Glenn was offered for disclosing the claimed dual expression cassettes. Applicant's summary of Glenn's disclosure is largely unrelated to the present invention and thus is shifting the focus away from the explicit suggestion of the art-recognized dual expression cassette vectors (page 8, paragraph [0073]) as well as codon optimization of HCV nucleic acids or polynucleotides for expression in mammalian cells (page 8, paragraph [0072]). Applicant de-emphasized the disclosure of dual expression cassettes in the Glenn publication by dismissing the disclosure as a simple statement. Regardless of the format of disclosure, one cannot deny the fact that Glenn specifically discloses that it is commonly known in the art to use dual expression cassettes in expression vectors and hence suggests dual cassettes for HCV polynucleotide sequences. Applicants then argue that Shah fails to disclose suggest dual expression cassettes. However, this component is disclosed by Glenn, which was applied as a secondary reference. Thus, the obviousness of the combination does not hinge on whether Chien or Shah suggests using two cassettes to express HCV core and other proteins. Rather, the combination of the references was to use the Glenn publication's double cassette technology to express the Chien patent's HCV core protein downstream from the HCV NS3-NS4B-NS5B and to replace the Chien patent's HCV core protein with the Shah's patent's truncated core protein, as indicated above.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to divide the HCV NS3-NS4B-NS5B-core sequence into two expression cassettes is immediately apparent to one skilled in the art, as suggested by Glenn.

Examiner further disagrees with Applicant's argument that the present invention is directed to immunogenic compositions that are capable of eliciting an immune response against HCV *in vivo*. Such an argument is not valid because the instant claims do not limit the immunogenic composition to *in vivo* immunogenicity. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., capable of eliciting an HCV specific immune response *in vivo*) are not recited in the rejected claims). Although the claims are interpreted in light of the specification, limitations from

the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Finally, in response to Applicant's argument that the arrangement of the first expression cassette encoding the core protein in cis downstream of the second expression cassette encoding other HCV protein(s) is not obvious, Examiner respectfully submits that both the Chien and Shah patents already disclose such order of insertion in a expression vector. Chien discloses the DNA cassette encoding HCV core *in cis* downstream from HCV NS3-NS4B-NS5B proteins. Shah discloses a plasmid containing codon-optimized sequences of an HCV core region of amino acids 1-150 downstream from an HCV NS3 segment *in cis*. Therefore, the prior art includes each claimed element and one skilled in the art would have recognized that the results of the combination, i.e. the expression level of the HCV proteins in a single cassette versus in two *cis* cassettes, were predictable.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
10 December 2008
/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648